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In re Patent Application of
Masashi KAMITAMARI et al.
Serial No.: 09/766,575 Group Art Unit: 1621
Filed: January 23, 2001 Examiner: Brian J. DAVIS
For: CHIRAL COPPER COMPLEX AND PRODUCTION PROCESSES THEREOF AND USING THE SAME

DECLARATION OF Koji HAGIYA UNDER 37 C.F.R. 1.132

Assistant Commissioner for Patents
Washington, DC 20231

I, Koji HAGIYA, a citizen of Japan, residing at 5-4-405, Gakuen-cho, Ibaraki-shi, Osaka, Japan do hereby declare and say that:

1. I am one of the joint inventors of the above identified application;
2. I received a Master degree in Chemistry from Tohoku University, Faculty of Science, Department of Chemistry in March 1986;
3. Since April 1986 up to present, I have been employed by Sumitomo Chemical Company, Limited and engaged in the research work on synthesis of agrochemical or pharmaceutical compounds;
4. I read the Office Action issued April 23, 2002, and the references, in particular USP 4,029,683 and USP 4,029,690 to Aratani et al. cited therein. The following experiments were conducted by the technicians of said Company under my direction and supervision to present comparative data to show the unexpected results of cyclopropanation reaction of the present invention.

Experiment

1. Cyclopropanation reactions were conducted by using the catalyst ligands of the present invention and ligands prepared from 5-chlorosalicylaldehyde, 3-nitrosalicylaldehyde and 3,5-dibromosalicylaldehyde that are position isomers or analogues of the ligands of the present invention and were disclosed at the last two lines of column 3 of USP 4,029,683 and at lines 10 to 12 of column 4 of USP 4,029,690 to Aratani.
   Salicylaldehyde was used as a representative example of Aratani et al.
   5-Fluorosalicylaldehyde was compared with 3-fluorosalicylaldehyde to show the effect of substitution position.

2. Catalysts preparation and Cyclopropanation reaction.

Experiment 1A Catalyst preparation

0.2227 g of (R)-N-(5-nitrosalycylidene)-2-amino-1,1-di(2-methoxyphenyl)-1-propanol, 0.0898 g of copper acetate monohydrate and 15 g of ethyl acetate were charged in a 100 ml glass flask, and the resulting mixture was reacted at 80℃ for 1 hr. After cooled to room temperature, the reaction solution was mixed with 0.2 g of a 28wt% sodium methylate/methanol solution, and stirred for 10 minutes. 5 g of water were added thereto and settled and separated in a separatory funnel. Ethyl acetate was added to the separated oil layer to adjust the catalyst concentration to 0.005 mol/l.

Experiment 1B Cyclopropanation reaction

30.6 g of 2,5-dimethyl-2,4-hexadiene, 2 ml of the catalyst solution prepared in Experiment 1A above and 2μg of phenylhydrazine were charged into a 100 ml Schlenk flask purged with nitrogen gas, and 5.18 g of 2,5-dimethyl-2,4-hexadiene solution containing 1.14 g of ethyl diazoacetate were added dropwise thereto at 80℃ over 2 hours. After stirring and maintaining the reaction mixture at the same temperature for 30 minutes, resulting reaction mixture was analyzed by gas-chromatography analysis, which revealed that ethyl

2,2-diemthyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate was obtained in a yield of 96.1%, and trans/cis ratio was 58/42. Optical purity of the product was analyzed by liquid-chromatography analysis, which showed that optical purity of the trans-isomer was 61.2%e.e and that of the cis-isomer was 50.6%e.e.

Experiments 2A,2B and 3A,3B.
Experiments were conducted in a similar manner as in Experiment 1A and 1B with the exception that 3,5-dichlorosalicylaldehyde, and 3-fluorosalicylaldehyde were used in place of 5-nitrosalicylaldehyde.The results are summarized in Table 1.

Experiment 4A Catalyst preparation

19.6 g (44.9 mmol) of (R)-N-(5-nitrosalicylidene)-2-amino-1,1-di(2-methoxyphenyl)-1-propanol, 8.96 g (44.9 mmol) of cupric acetate, and 160 g of toluene were mixed in a flask and reacted at 80℃ for 1 hr under stirring. 100 g of n-heptane were added to the reaction solution to precipitate blue-green chrystals. The precipitated reaction mixture was cooled to 10℃ and filtered to collect the crystals. Collected crystals were washed with 100 g of n-heptane, and dried at room temperature to give 22.1 g of a copper complex of (R)-N-(5-nitro-salicylidene)-2-amino-1,1-di(2-methoxyphenyl)-1-propanol in a yield of 99.0%.

Experiment 4B Cyclopropanation reaction

33.06 g (300mmol) of 2,5-dimethyl-2,4-hexadiene, 4.97 mg (0.01 mmol) of a copper complex of (R)-N-(5-nitrosalicylidene)-2-amino-1,1-di(2-methoxyphenyl)-1-propanol obtained in Experiment 4A were charged in a 100 ml Schlenk tube purged with nitrogen gas and 4 μg of phenylhydrazine was added thereto. 1.14 g (10 mmol) of ethyl diazoacetate was added the resulting solution over 2 hrs and stirred at the same temperature for 30 min. The gas chromatography analysis of the reaction solution showed that the yield of chrysanthemate was 97.6 %, trans/cis ratio was 58/42. High-performance liquid chromatography analysis showed that optical purity of the trans-isomer was 63 % e.e and cis-isomer

was 57 % e.e.

Experiment 5A Catalyst preparation

0.46 g of a copper complex of (R)-N-(3,5-dichlorosalicylidene)-2-amino-1,1-di(2-methoxyphenyl)-1-propanol was obtained in a yield of 97.9% according to a similar manner as in Example 4A except that 0.415 g (0.901 mmol) of (R)-N-(3,5-dichlorosalicylidene)-2-amino-1,1-di(2-methoxyphenyl)-1-propanol was used in place of (R)-N-(5-nitrosalicylidene)-2-amino-1,1-di(2-methoxyphenyl)-1-propanol and 0.180 g (0.901 mmol) of cupric acetate, 10 g of toluene, 10 g of n-heptane for precipitation of the crystals, 10 g of n-heptane for washing the crystals were used.

Experiment 5B Cyclopropanation reaction

Chrysanthemate was produced in a similar manner as in Experiment 4A in a yield of 97.6 %, where trans-cis ratio was 60/40, trans-isomer was 61 % e.e and cis-isomer was 56 % e.e. except that 5.22 mg (0.01 mmol) of a copper complex of (R)-N-(3,5-dichlorosalicylidene)-2-amino-1,1- di(2-methoxyphenyl)-1-propanol was used in place of 4.97mg of a copper complex of (R)-N-(5-nitro-salicylidene)-2-amino-1,1-di(2-methoxyphenyl)-1-propanol.

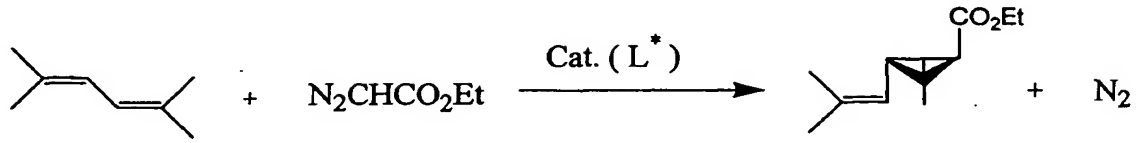
Comparative Experiments 1 to 5

Experiments were conducted in a similar manner as in Example 1A and 1B except that 5-chlorosalicylaldehyde, 5-fluorosalicylaldehyde, 3-nitrosalicylaldehyde, 3,5-dibromosalicylaldehyde and salicylaldehyde were used in place of 5-nitrosalicylaldehyde. The results are summarized in Table 1 below.

Comparative Experiment 6 Catalyst Preparation

1.0 g (2.56 mmol) of (R)-N-salicylidene-2-amino-1,1-diphenyl-propanol and 0.511 g (2.56 mmol) of cupric acetate were mixed in 5 g of toluene and reacted at 80℃ for 1 hr under stirring. Then 50 g of n-heptane was added thereto and cooled to 10℃, which produced no precipitated product and remained as a clear solution.

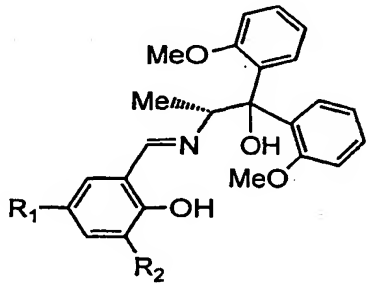
Table 1 Comparison of the effect of ligands in Cyclopropanation Reaction



Exp. No.	L*		Amount of Cat *	Yield	t/c	Optical purity、%e. e.	
	R_1=	R_2=	mol%	%		t	c
Ex. 1B	NO_2	H	0. 10	96. 1	58/42	61. 2	50. 6
Ex. 2B	Cl	Cl	0. 05	94. 2	60/40	65. 3	59. 8
Ex. 3B	H	F	0. 10	96. 9	59/41	61. 7	56. 5
Ex. 4B	NO_2	H	0. 10	97. 6	58/42	63	57
Ex. 5B	Cl	Cl	0. 10	97. 6	60/40	61	56
Comparative Ex. 1	Cl	H	0. 10	96. 1	59/41	55. 8	51. 1
Comparative Ex. 2	F	H	0. 10	96. 0	60/40	42. 8	41. 1
Comparative Ex. 3	H	NO_2	0. 10	97. 3	59/41	54. 5	48. 3
Comparative Ex. 4	Br	Br	0. 10	98. 0	60/40	55. 1	57. 8
Comparative Ex. 5	H	H	0. 10	95. 4	60/40	38. 4	37. 6

Catalyst preparations were conducted in the same way as in Catalyst preparation Example 1A with the exception of Ex.4B and 5B.

L*: Employed Ligand



Conclusion

As can be seen from the reaction results shown in Table 1 above, optical purity of the product obtained by the presently claimed process using the catalyst comprising the ligand are superior as compared to the optical purity of the cyclopropanation product obtained by the process based on the teachings of Aratani et al by mere differences of positions of the substitution or the kind of substituents on the salicilydene moiety of the catalyst ligands.

Thus, unexpected results of the presently claimed processes using the presently claimed chiral ligand compounds are shown by the experiments above over the teachings of Aratani et al.

The undersigned declares further that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fined or imprisonment, or both under 18 U.S.Code 1001 and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

This 13th day of March 2003

Koji Hagiya

Koji HAGIYA